Prediction Accuracy of Allometric Approaches for Macromolecules: Application for Biosimilar Development

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Background & Purpose

In the development of biosimilar compounds the objective is to demonstrate a high degree of similarity to a reference biologic. Establishing similar pharmacokinetic properties between two compounds is vital prior to confirmation of similar clinical safety and efficacy.

Interspecies scaling of animal pharmacokinetics (PK) to human can potentially improve selection of biosimilar candidates prior to conducting human trials.

Historically, reports evaluating prediction accuracy of interspecies scaling methods measured prediction success as the number of compounds within a 2-fold threshold. A 2-fold threshold may be too liberal for application to biosimilar development as scaling animal PK to human in this case calls for more precise estimation to improve confidence in terms of PK similarity prior to proceeding to clinical development.

The purpose of this study is to identify the most accurate allometric-type interspecies clearance (CL) scaling approach for use in guiding biosimilar development.

Methods

Literature reports evaluating prediction accuracy of interspecies scaling for CL of macromolecules was reviewed. Omitted were reports that included:

- methods that considered adjustments for physico-chemical properties
- methods that considered adjustments for in-vitro metabolism data and/or protein binding
- reports using < 5 compounds
- Prediction accuracy of oral CL (since all currently available biologics are marketed only in parenteral form)

Prediction accuracy was performed for scaling methods in **Table 1** using:

1. Absolute average fold-error (AAFE) was used to assess the prediction success across a group of compounds where AAFE = $10[\sum|\log \text{fold-error}/n|]$

2. Proportion of observations (i.e. compounds) where the prediction accuracy fell within the range 0.7-1.3 fold-error.

Table 1: Methods for the prediction of human clearance

Interspecies Method (reference)	Formula	Notes
Simple Allometry		
≥3 Species (Mordenti 1991 *Pharm Res* 8(11):1351-1359)	$\log y = \log a + (b) \log * W$	Use ≥50-fold weight range for species
Maximum Lifespan Potential (MLP) Correction (Boxenbaum 1984 *Drug Metab Rev* 15(5&6):1071-1121)	CL x MLP	Correct observed animal clearance prior to plotting in simple allometry
Brain Weight (BW) Correction (Boxenbaum 1984 *Drug Metab Rev* 15(5&6):1071-1121)	CL x BW	
Rule of Exponents (ROE) (Mahmood 1996 *Xenobiotica* 26: 887-895)	When 0.55<b<0.7 use simple allometry; 0.71<b<0.99 use MLP; b≥1 use BW	Prediction error may not be acceptable when b<0.5 or >1.3; MLP not recommended; macromolecules; use BW when b≥1 (Mahmood 2009 *J Pharm Sci* 98: 3850-3861)
Species-Invariant Time Techniques		
Kallynochrons (Elementary Dedrick) (Boxenbaum 1984 *Drug Metab Rev* 15(5&6):1071-1121)	y-axis = concentration/(Dose/W); x-axis = time/W^{1-b}	b and c are the exponents derived from ≥3 species using simple allometry for CL and V
Apolysichrons (Complex Dedrick) (Boxenbaum 1984 *Drug Metab Rev* 15(5&6):1071-1121)	y-axis = concentration/(Dose/W^c); x-axis = time/W^{c-b}	
"Simplified" Allometry		
Single Species Fixed Exponent (Ling et al. 2009 *J Clin Pharmacol* 49: 1382-402)	$CL_{human}=CL_{animal}\ (W_{human}/W_{animal})^b$	
Two-Species Allometric Techniques		
Two-species fixed coefficient with optimized or fixed Exponent (Tang 2007 *Drug Metab Dispos*. 35 1886-1893)	$CL_{human}=a_{two\text{-}species}\ (W_{human})^b$	

Results

- AAFE values and the proportion of compounds within the range of 0.7-1.3 are presented in **Table 2**
- Of the methods reviewed, traditional simple allometry with a minimum of 3 species with or without the rule of exponents performed inconsistently with some comparisons resulting in >2-fold-error
- The proportion where the prediction accuracy was within the range of 0.7-1.3 varied from as low as 16 % of compounds tested to as high as 100 %.

Discussion

- Most literature reports of single-species interspecies scaling approaches evaluated prediction accuracy of compounds in the monoclonal antibody class
- Monkeys were most frequently cited as the species employed in simplified allometric approaches
- Fixed exponents for simplified allometric approaches of CL ranged from 0.7-0.95
- Simplified allometric approaches with fixed exponents typically resulted in a high proportion of compounds within the range of 0.7-1.3.
- Exponents values ≥0.8 and ≤0.9 tended to result in lower AAFEs and a higher proportion of compounds within the tighter acceptance range of 0.7-1.3

Table 2: Comparison of interspecies scaling approaches for clearance

Reference	Therapeutic Classification	Interspecies Scaling Approach	Number (N) of Compounds	AAFE	Number (N) within 0.7-1.3 fold-error
Mordenti et al. 1991 *Pharm Res* 8:1351-9	Various therapeutic proteins	Simple allometry [a]	5	1.16	5
Mahmood 2009 *J Pharm Sci* 98: 2472-93	Various therapeutic proteins	Simple allometry [a]	6	2.05	2
		Maximum Lifespan Potential (MLP) [b]	6	3	1
		Brain weight (BW) [c]	6	4.6	1
		Single species mouse, fixed exponent 0.75	6	1.77	1
		Single species rat, fixed exponent 0.75	5	1.77	1
Mahmood 2009 *Haemophilia* 15: 1109-17	Coagulation factors; Tissue-type plasminogen activators	Simple allometry [a]	5	1.25	5
		2-Species Rat-Dog	5	1.40	3
Dong et al. 2011 *Clin Pharmacokinet* 45: 1013-34	Monoclonal antibody (mAb)	Single species Monkey, fixed exponent 0.75	10	1.56	4
Ling et al. 2009 *J Clin Pharmacol* 49: 1382-402	mAb	Single species Monkey, fixed exponent 0.75	13	1.54	3
		Single species Monkey, fixed exponent 0.80	13	1.38	8
		Single species Monkey, fixed exponent 0.85	13	1.26	11
		Single species Monkey, fixed exponent 0.90	13	1.18	11
		Single species Monkey, fixed exponent 0.95	13	1.23	11
		Single species Monkey, Dedrick, fixed exponent 0.8	6	1.36	4
		Single species Monkey, Dedrick, fixed exponent 0.85	6	1.29	5
		Single species Monkey, Dedrick, fixed exponent 0.90	6	1.24	4
Oitate et al. 2011 *Drug Metab PK* in press	mAb soluble target mAb membrane-bound target	Single species Monkey, Dedrick, fixed exponent 0.79	6	1.55	2
		Single species Monkey, Dedrick, fixed exponent 0.96	6	1.45	3
Deng et al. 2011 *MAbs* 3: 61-6	mAb	Simple allometry [a]	11	1.91	1
		Rule of Exponents	8	1.64	0
		Single species Monkey, fixed exponent 0.85	13	1.18	11

[a] SA= simple allometry with ≥ 3 species not including human; [b] MLP= Clearance x Maximum Life-Span Potential; [c] BW= Clearance x Brain Weight

Conclusions

For macromolecules, and particularly monoclonal antibodies, employing single-species monkey "simplified" allometric approaches with a fixed exponent of 0.85 may be more appropriate than traditional allometric approaches in predicting human CL.